

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 5

at, *inter alia*, page 41, line 3 through to page 42 line 9; page 52, lines 22-25; and page 53 line 25 through page 54, line 4. Support for new claim 50 can be found in the specification at, *inter alia*, page 31, lines 6-15. Support for new claim 51 can be found in the specification at, *inter alia*, page 31, line 12; page 41, lines 6-14; and page 52, lines 22-25. Support for new claim 52 can be found in the specification at, *inter alia*, page 41, lines 6-14 and page 28, lines 3-13. Support for new claim 53 can be found in the specification at, *inter alia*, page 28, line 26 through page 29, line 20; page 51, lines 5-18; and page 53, line 12 through page 54, line 27. Support for new claim 54 can be found in the specification at, *inter alia*, page 51, lines 1-5 and page 27, line 30 through page 28, line 32. Support for new claim 55 can be found in the specification at, *inter alia*, page 27, line 30 through page 28, line 1. Support for new claims 56-58 can be found in the specification at, *inter alia*, page 32, lines 8-26. Support for new claims 59 and 60 can be found in the specification at, *inter alia*, page 32, lines 1-6; page 37, lines 10 and 11; and page 37, lines 22-30. Support for new claims 61-63 can be found in the specification at, *inter alia*, page 33, lines 15-24 and page 37, lines 1-21. Finally, support for new claim 64 can be found in the specification at, *inter alia*, page 27, line 4 through page 28, line 33; page 29, lines 11-20; page 38, lines 27-34; page 50, line 20 through page 51, line 20; and page 53, line 11 to page 54, line 4.

The remaining changes to the claims merely introduce additional grammatical and format changes. Applicants maintain that these amendments raise no issue of new matter.

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 6

In view of the arguments set forth below, applicants maintain that the rejections made in the April 10, 2001 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides new methods for transplanting xenogeneic cells and tissues. These methods are characterized by the use of an immunoglobulin-impermeable membrane to surround transplanted cells or tissues, and the administration of an agent which inhibits an immune system costimulation event. The claimed methods are surprisingly advantageous, in that they greatly prolong the survival of transplanted xenogeneic cells and tissues in a subject.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1, 2, 4-7, 9-14, 16, 17, 20, 23 and 43-47 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. Applicants understand this rejection to be directed to new claims 48-64.

In response, applicants respectfully traverse the Examiner's rejection.

The Examiner asserted that the claims as written are not limited to defined co-stimulation events.

Contrary to the Examiner's position, however, claims 48-63 provide a

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 7

method wherein the agent administered inhibits a costimulation event mediated by one of several enumerated cell surface molecules. Specifically, as recited in claim 48, these cell surface molecules include B7, CD28, CTLA4, GP39, CD40 and CD4. Thus, applicants maintain that one of skill would know how to practice this method.

As for the method of claim 64, applicants note that nowhere in this claim is the phrase "costimulation event" recited. The Examiner's assertion is therefore obviated by the language of this claim.

In view of the above remarks, applicants maintain that claims 48-64 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 1, 2, 4-7, 9-14, 16, 17, 20, 23 and 43-47 under 35 U.S.C. §103 as allegedly obvious over Lenschow et al., in view of Goosen et al., Soon-Shong et al., Akalin et al., Linsley et al., Padrid et al. and Steurer et al. Applicants understand the rejection as directed to new claims 48-64.

In response, applicants respectfully traverse the Examiner's rejection, and maintain that the Examiner has failed to make a *prima facie* case of obviousness.

Again, the instant transplantation methods are characterized in relevant part by two features. The first feature is the use of a xenogeneic cell or tissue for transplantation. The second feature is the combination of two steps which hitherto have never been

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 8

performed together in a transplantation procedure -- i.e., (i) the use of a *semi-permeable membrane* to surround transplanted cells and tissues and (ii) the administration of a *costimulatory event-inhibiting agent*. The instant methods are surprisingly effective.

Each of the cited references above teaches nothing more than the use of a semi-permeable membrane or a costimulatory event-inhibiting agent, *but not both*. That is, Goosen et al. and Soon-Shong et al. teach cell microencapsulation. Lenschow et al., Akalin et al., Linsley et al., and Steurer et al. teach the use of CTLA4Ig in connection with transplantation. Finally, Padrid et al. teach the use of CTLA4Ig in conjunction with asthma.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. To support such a case, the cited references, taken together, would at the very least have to create a reasonable expectation that the claimed invention would have the superior qualities it in fact possesses.

This they fail to do.

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 9

The claimed methods of xenogeneic transplantation are surprisingly advantageous. Indeed, these methods succeed to a far greater degree than do xenogeneic transplantation methods employing either a semipermeable membrane or inhibitory agent alone.

Table 8, on page 92 of the specification, underscores this point. Briefly, this table shows data from xenotransplantation experiments performed by transplanting (i.e. grafting) porcine cells into mice. In relevant part, the table shows three sets of data. The first set (row 1) shows graft survival (in days) using microencapsulation of cells ("MC/IP") without an inhibitory agent. The second set (row 4) shows graft survival using an inhibitory agent ("CTLA4Ig") without microencapsulation ("splenic"). Finally, the third set (row 2) shows graft survival using both microencapsulation and the inhibitory agent CTLA4Ig.

The resulting synergy between microencapsulation and CTLA4Ig is *dramatic and most unexpected*. Graft survival with CTLA4Ig alone was a mere 5 days. Graft survival with microencapsulation alone was 27 days. However, graft survival with both CTLA4Ig and microencapsulation together was no fewer than 115 days -- *over 4-fold longer* than with microencapsulation alone and *over 20-fold longer* than with CTLA4Ig alone. Nothing in any of the cited references would permit one of ordinary skill to foresee such an unexpected outcome.

For these reasons, the Examiner has failed to establish the *prima facie* obviousness of claims 48-64 over the cited references. For the same reasons, applicants alternatively maintain that the rejected

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 10

claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 48-64 satisfy the requirements of 35 U.S.C. §103.

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly allowance is respectfully requested.

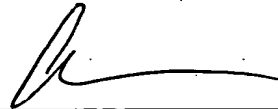
If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this

Applicants: Collin J. Weber, et al.
Serial No.: 09/049,865
Filed: March 27, 1998
page 11

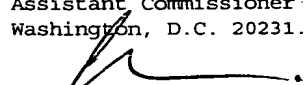
Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents,
Washington, D.C. 20231.


Alan J. Morrison
Reg. No. 37,399

7/9/01 Date

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. No. (212) 278-0400